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14. ABSTRACT The study comprises a randomized two-arm, single center clinical trial conducted at the Department of Orthopaedic Surgery & Rehabilitation, University of Texas Medical Branch, Galveston, TX, with a primary objective to assess and compare the functional outcome of patients with large segmental bone defects reconstructed with the Masquelet technique (MT) versus the titanium mesh cage technique (TMCT). The secondary objectives include the radiographic determination of defect healing, and comparative assessment of cost and resource expenditures between the two techniques. From 9 patients with segmental defects presented to our institution over the initial 12-month trial period, 4 met the study eligibility criteria and were enrolled: 1 MT, 2 TMCT, 1 voluntary withdrawal from surgical treatment. One MT-treated patient had a defect due to a close-range, high-caliber gunshot injury to the distal femur, and at 5-month followup demonstrates very successful functional and radiographic outcome. One TMCT-treated patient had an iatrogenic resection of an infected nonunion of the humerus mid-shaft, and at 1-month followup demonstrates uneventful healing. A second TMCT-treated patient with an iatrogenic resection of proximal tibia osteomyelitis had a serious adverse event. At 2 weeks post TMCT reconstruction, the patient developed significant tissue necrosis over the defect which resulted in an above-knee amputation as per the patient's request. There are 2 additional eligible patients who are currently in pre-reconstruction phase of the defect management. Eligible patient identification and enrollment for the trial is actively ongoing.					
15. SUBJECT TERMS Segmental bone defects reconstruction; Masquelet technique; Titanium mesh cage technique					
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1. Introduction

A United States Department of Defense grant funds the present clinical study which can be a major improvement in the treatment of extremity trauma involving segmental bone loss. These devastating injuries occur in both civilians and the military setting, and typically result from motor vehicle accidents, high-energy fractures, gunshot injuries, and blast injuries, but also from iatrogenic resections of a bone segment due to infection or tumor. Despite many recent advances in this area, it remains extremely difficult to achieve adequately bone defect healing and restore limb pre-injury function. Standard treatment options are exceedingly complex, require highly specialized equipment and/or skills, and typically require multiple surgical procedures over a protracted period of time. Moreover, major complications frequently occur with all the standard options, the patient's ability to return to acceptable limb functional is typically low, and, in many instances culminates in amputation.

The present clinical study addresses this issue by assessing and comparing two new Food & Drug Administration (FDA)-approved, innovative surgical bone defect treatment techniques that can be significantly more effective for civilian and military patients with these conditions. One treatment method—the Masquelet Technique—involves two-stage surgery; the first stage induces a biomembrane around the defect following the application of a cement spacer, and at 6-8 weeks later the second stage consists of cement spacer removal and bone graft placement while preserving the biomembrane. The other method, developed by the study primary investigators (PIs)—the Cage Technique—comprises one-stage surgical procedure in which a cylindrical, fenestrated, titanium cage packed with bone graft is implanted in the defect. Initial clinical experience with both of these techniques has been very promising, and until recently, there has been no prospective clinical study comparing these two novel defect treatment methods.

The present study is a randomized two-arm, single center clinical trial conducted at the Department of Orthopaedic Surgery & Rehabilitation, The University of Texas Medical Branch (UTMB) in Galveston, Texas. The trial primary objective is to assess and compare the functional outcome of patients with large segmental bone defects reconstructed with the Masquelet Technique versus the Cage Technique. The trial secondary objectives include the radiographic determination of defect healing, and the comparative assessment of cost and resource expenditures between the two techniques.

2. Keywords

Critical-size bone defects;
Segmental bone defect reconstruction;
Masquelet technique;
Titanium mesh cage technique

3. Overall Project Summary

Study Initiation and Approvals: The clinical trial was initiated with acquiring all necessary UTMB Institutional Review Board (IRB) approvals to conduct the study. The first study IRB application was submitted on Apr 26, 2013, and was approved with stipulations which were subsequently addressed gaining the full IRB approval (IRB 13-100) to conduct the study beginning on Oct 31, 2013 until April 26, 2014. In order to enhance the study patient enrollment, an IRB application was filed on Feb 19, 2014 to include the civilian prisoners who are routinely treated in the PIs UTMB clinical facility as the eligible study subjects. The UTMB IRB

disapproved the inclusion of the civilian prisoners as a study subjects justifying it as not meeting criteria outlined under UTMB policy 45 CFR 46 Subpart C, 46.306(a)(2)(iv), specifically identifying the following reasons: a) utilizing this vulnerable population in order to increase enrollment; b) this subject population who undergo the Masquelet procedure may have a difficult recovery while being incarcerated; and c) one group may have more benefits than the other since this study compares the two standard of care procedures. Although the PIs disagreed with the IRB justification of this disapproval, it was determined that the PIs would appeal the IRB decision of disapproving after collecting and reviewing the initial trial results (ie, 12 months). Subsequently the UTMB IRB application for continuing the trial involving the UTMB non-prison patients as study subjects was filed on Feb 25, 2014, and full approval was obtained on Apr 13, 2014 with the validity until Mar 28, 2015. EntryPoint i4 software was obtained and the trial-specific case review forms (CRFs) generated. Patient reimbursement for study participation and respective follow clinic visit was changed from check in-mail to gift card streamline the process. The study's protocol and informed consent were amended accordingly, and the changes approved by the UTMB IRB.

Patient Enrollment and Followup: Overall, the patient enrollment in the trial has been sluggish, and at a slower rate than anticipated as indicated in the Projected the Quarterly Enrollment of initially submitted SOW. Over the last 12-month trial period, a total 9 patients with segmental defects presented to our institution. Among these patients were 3 civilian prisoners who otherwise met the study eligibility criteria, and 2 non-prison patients with segmental defects who did not meet the study inclusion/exclusion criteria. The remaining 4 non-prison patients met the study eligibility criteria, and they were all successfully enrolled, and subsequently randomized to the respective study treatment arms. These patients include:

- (1) A 36-year old female with a protracted infected proximal tibia nonunion treated with iatrogenic resection of the infected bone segment. This patient was randomized to study Arm II and received the Cage Technique in combination with allograft cancellous croutons-demineralized bone matrix (DBM) composite (Option B). The surgical procedure was uneventful, and the patient was discharged from hospital. At 2 weeks post defect reconstruction, the patient reported surgical wound healing issues in a telephone conversation. Despite being informed about the serious nature of the concerns and urged to return for immediate evaluation, the patient failed to comply. At 3 weeks post defect surgery, the patient presented to our ER with a wound dehiscence, and was immediately admitted to the hospital. The wound was surgically irrigated and debrided (I&D), a wound-vac applied, systemic antibiotic therapy initiated, and the patient was eventually discharged with good prognosis. The patient's failure to attend multiple scheduled clinic visits continued. A social worker reported that the patient was not compliant with the antibiotic therapy, abused illegal substance/drugs, and continued smoking despite being informed about its adverse effects on wound and defect healing. At 2 months post last hospital admission, patient presented to the ER again with wound drainage, and extensive skin necrosis over the defect. At that time, the patients requested the limb amputation despite being repeatedly offered the several limb salvage options. The patient wound complication was reported as a serious adverse event (SAE) to the UTMB IRB and the DoD, and the patient was withdrawn from the study.
- (2) A 66-year-old male with segmental bone loss in the distal femur due to a close-range, high-caliber civilian gunshot injury. This patient was randomized to study Arm I and received the two-stage Masquelet Technique in combination with a Reamer-Irrigator-Aspirator (RIA)-harvested bone graft (Option A) according to the study protocol. The patient completed all the required study followup visits, and is currently at 5-month post index defect surgery.

The patient's followup has been uneventful to date, and he demonstrated very successful functional and radiographic outcome.

- (3) A 62-year-old male with an infected femur shaft nonunion/malunion was enrolled in the study and randomized to the study Arm II. Prior to the scheduled surgery that was to consist of nonunion resection and defect reconstruction, the patient voluntarily left hospital and has not returned for followup and cannot be contacted.
- (4) A 44-year-old female) with humerus chronic osteomyelitis that has resulted in diaphyseal bone deficiency was enrolled to the study and randomized to the study Arm II. The patient received the Cage Technique for defect reconstruction in combination with allograft cancellous croutons-DBM composite (Option B). The patient is currently at 2 weeks post defect reconstruction and the healing course to date has been uneventful.

Enhancement of Study Enrollment: The study PIs identified 2 additional eligible patients who are now in the pre-reconstruction phase of their defect management. These patients have been informed about study participation, and their successful enrollment is expected once they are suitable (ie, in 3-4 weeks) for the surgical defect reconstruction.

Eligible patient identification and enrollment for the trial is actively ongoing. Furthermore, the PIs have discussed the prospect of satellite center participation with several local Level I trauma Hospitals (eg, Ben Taub, Memorial Hermann), and thereby enhance the enrollment of the eligible patients. The assessment of the prospective number of eligible patients potentially offered by these hospitals is not actively ongoing, and when completed, it will be presented to the DoD for consideration of adding them as the additional trial sites.

4. Key Research Accomplishments

The study is ongoing.

Study UTMB IRB approvals/amendments/renewals.

Planning and executing the trial as per the IRB-approved protocol has been optimized, and all study team members became familiar with their roles and responsibilities in conducting the trial.

5. Conclusion

The study enrollment has been sluggish. Solutions to enhance patient accrual will include: a) an inclusion of civilian prison patients by appealing the UTMB IRB disapproval and its justification; b) familiarizing the regional physicians with the trial, and enhancing their referral of eligible patients to the UTMB trial sites; c) potential inclusion of non-UTMB Level I trauma hospitals (Ben Tub, Memorial Hermann) as a study sites.

Initial functional and radiographic outcomes of limb/defect healing for patients treated with the Masquelet (Arm I) and the Cage (Arm II) technique are very favorable.

The SAE experienced in one patient as the study subject was primarily due to lack of compliance with the treatment, physician's recommendations, and not attending followup clinic visits as per study protocol. Any signs of noncompliance in otherwise eligible patients as prospective study subjects will be considered as a major exclusion criterion.

Utilizing the UTMB's EPIC electronic medical records facilitates planning the patient's followup clinic visits, informing/reminding the enrolled patients about the study participation and filling out the questionnaires. Gift card reimbursement streamlines and simplifies the process of patient reimbursement for study participation and followup visits.

6. Publications, Abstracts, and Presentations

Lindsey RW & Gugala Z. The Comparative Efficacy of the Masquelet Technique versus Titanium Mesh Cage Technique in the Reconstruction of Segmental Bone Defects. A DoD-UTMB Clinical Trial. MD Anderson Grand Round Talk, Houston, TX, on Nov 7, 2013.

Lindsey RW & Gugala Z. The Comparative Efficacy of the Masquelet Technique versus Titanium Mesh Cage Technique in the Reconstruction of Segmental Bone Defects. A DoD-UTMB Clinical Trial. UTMB Grand Rounds, Houston, TX, on Nov 26, 2013.

Lindsey RW & Gugala Z. The Comparative Efficacy of the Masquelet Technique versus Titanium Mesh Cage Technique in the Reconstruction of Segmental Bone Defects. A DoD-UTMB Clinical Trial. Baylor College of Medicine Grand Rounds, Houston, TX, on Oct 10, 2014.

7. Inventions, Patents and Licenses

Nothing to report.

8. Reportable Outcomes

Nothing to report.

9. Other Achievements

Nothing to report.

10. References

Nothing to report.

11. Appendices

Nothing to report.